REMARKS

Upon entry of the instant Amendment and Response, claims 1 and 50-59 are pending in the above-referenced application. Claims 2-49 were previously cancelled. Claims 56 and 59 are withdrawn from consideration since they are drawn to non-elected species.

Applicants acknowledge the Examiner's statement that the formal drawings, filed November 27, 2002 (Paper No. 25), are in compliance with 37 C.F.R. § 1.84.

I. Amendments to the Specification

Without acquiescing to the Examiner's allegation that the priority of the instant claims appears to be USSN 08/253,964 and not the earlier applications, Applicants have amended the specification to update the relationship and status of the priority documents, purely to expedite the prosecution of the instant application. Applicants thank the Examiner for pointing out that the priority document "08/253,694" should have been listed as "08/253,964"; this typographical error has been corrected in the current amendment to the specification.

The specification has also been amended to correct minor clerical errors relating to the ES5.2D8 monoclonal antibody. Support for the amendments can be found throughout the application as filed and specifically at page 18, lines 16-38 to page 19, line 1; and page 19, line 14-16. It is submitted that no new matter has been added.

The specification has been further amended to correct any improper usage of trademarks. Trademarks have been capitalized and accompanied by the ™ or ® symbols wherever they appear.

II. Amendments to the Claims

Claim 1 has been amended; support for this amendment can be found specifically at page 33, lines 7-34; page 35, lines 9-38 and continuing on page 36, lines 1-27. No new matter has been added as a result of the current amendment.

Claims 56 and 59 have been withdrawn from consideration as being drawn to non-elected species.

III. Amendments to the Drawings

The legend in Figure 17 has been amended to correct minor clerical errors. Support for the amendments can be found throughout the application as filed and specifically at page 18, lines 16-36 to page 19, line 1; and page 19, line 14-16. It is submitted that no new matter has been added.

IV. Clarification of Ownership

The Examiner requested clarification regarding the ownership of the claimed invention to consider patentability of the claims under 35 U.S.C. § 103(a) (Office Action, page 4, section 7). Applicants believe that the current inventorship of claims 1 and 50-59 is proper. Thus, a potential rejection under 35 U.S.C. § 103(c) and under 35 U.S.C. § 103 (a) has been rendered moot.

V. Rejection under 35 U.S.C. § 102(b)

Claim 1 stands rejected under 35 U.S.C. § 102(b), for allegedly being anticipated by Ledbetter et al. (J. Immunol. 137:3299-3305, 1986) (Office Action, page 4, paragraph

8). The Examiner relies on Ledbetter et al. to teach "methods of activating the proliferation of T cells with anti-CD3 and anti-Tp44 antibodies" (Office Action, page 4, paragraph 8). Applicants respectfully traverse the foregoing rejection and request reconsideration.

To anticipate a claim, a prior art reference must disclose each and every limitation of the claimed invention, either explicitly or inherently. See *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). Absence of a claim element from a prior art reference negates anticipation. *Atlas Powder Co. v E. I. du Pont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984)*. Anticipation of a patent claim requires a finding that the claim at issue "reads on" a prior art reference. See *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781, 227 USPQ (BNA) 773, 778 (Fed. Cir. 1985). In other words, if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether it also covers subject matter not in the prior art. *See id.* at 781.

Upon entry of the current amendment to the claims, claim 1 is directed to a method for inducing a population of T cells to proliferate to sufficient numbers for use in therapy by activating a population of T cells; and by stimulating an accessory molecule on the surface of the T cells with a ligand which binds the accessory molecule, the activating and stimulating steps thereby inducing proliferation of the T cells to sufficient numbers for use in therapy.

Applicants respectfully submit that Ledbetter et al. do not teach or suggest each and every element of claim 1. Ledbetter et al. disclose that "T cells will proliferate if they are co-stimulated with anti-CD3 Sepharose and interleukin 1 or with monoclonal antibodies to the differentiation antigens CD5 or Tp44" (page 3299, right column, first paragraph). The focus of this reference is the finding that the functional and

biochemical mechanisms of CD5 and Tp44 signal transmission are distinct (page 3299, Abstract). Ledbetter et al. teach that antibody binding to Tp44 overcomes suppression of T cell proliferation by agents that increase the concentration of intracellular calcium whereas antibody binding to CD5 does not. In striking contrast, anti-CD5 causes an increase in cytoplasmic calcium free levels whereas Tp44 had no effect (page 3302, right column, last paragraph to page 3303, right column, first paragraph).

Nowhere in Ledbetter et al. is there a teaching or suggestion for Applicants' claimed method of inducing a population of T cells to proliferate ***to sufficient numbers for use in therapy*** by activating a population of T cells and by stimulating an accessory molecule on the surface of the T cells with a ligand, which binds the accessory molecule. Ledbetter et al.. do not explicitly or inherently teach the method of inducing a population of T cells, as claimed by Applicants', to sufficient numbers for use in therapy. There is no appreciation anywhere in this reference for the use of an induced population of T cells for use in therapy.

Since Ledbetter et al. fail to teach or suggest ***each and every*** element of claim 1, Applicants respectfully request that the rejection made under 35 U.S.C. § 102(b) be withdrawn.

VI. <u>Rejections under 35 U.S.C. § 102(e)</u>

Claims 50-55 stand rejected under 35 U.S.C. § 102(e), as purportedly being anticipated by Ledbetter et al. (U.S. Patent No. 6,010,902) (Office Action, page 4, paragraph 9). Applicants respectfully traverse the foregoing rejection and request reconsideration.

Specifically, the Examiner relies on Ledbetter et al. to teach "compositions comprising heteroconjugates or bispecific antibodies comprising antibodies, including

antibodies to human CD antigens involved in T cell activation, including antibodies to CD3 in combination with anti-CD28 antibodies (*e.g.* 9.3), including compositions in order to stimulate T cell populations and subpopulations and reinfused in patients" and for teaching that "these cell populations have increased signal transduction, which can be measured by various known assays." The Examiner is of the opinion that "the claimed functional limitations would be inherent properties of the referenced methods to stimulate T cell populations with heteroconjugates comprising anti-CD3 and anti-CD28 antibodies." As provided above, in order to anticipate a claim, a prior art reference must disclose ***each and every limitation*** of the claimed invention, either explicitly or inherently.

Claim 50, and claims depending therefrom, are directed to methods for inducing *ex vivo* proliferation of a population of T cells by contacting them with a solid phase surface immobilized with a first agent which provides a primary activation signal to the T cells, thereby activating the T cells; and a second agent which stimulates an accessory molecule on the surface of the T cells, thereby stimulating the activated T cells, the first and second agents thereby inducing the T cells to proliferate.

Applicants respectfully submit that Ledbetter et al. do not teach or suggest each and every element of claims 50-55. Rather, Ledbetter et al. teach novel antibody heteroconjugates and bispecific antibodies and their use in the enhancement or inhibition of activation and function of T and B lymphocytes (column 1, lines 19-22). Therefore, this reference provides no explicit or inherent teaching or suggestion for a method of inducing *ex vivo* proliferation of a population of T cells by contacting the T cells with a solid phase surface having a first and second agent directly immobilized thereon.

Bispecific antibodies, as disclosed by Ledbetter et al., are "comprised of a first binding region reactive with a first surface antigen expressed on lymphocytes and a second binding region reactive with a second lymphocyte antigen on the same cell" (column 6, lines 35-38). "They are prepared by fusing various hybridoma cell lines producing mAb reactive with CD antigens" (column 32, lines 1-3). Applicants respectfully assert that bispecific antibodies do not read on "agents directly immobilized on a solid surface" of the instant application. Bispecific antibodies are a modification of an antibody to possess two different antigen binding domains; they do not in any way explicitly or inherently disclose two agents immobilized on a solid surface.

Heteroconjugates, according to Ledbetter et al., are comprised of at least two antibody molecules cross-linked to each other, each molecule being reactive with a different lymphocyte antigen on the same cell (Abstract [57], lines 4-7). They are prepared as described below:

> The two monoclonal antibodies were conjugated at a 1:1 molar ratio with the heterobifunctional cross-linking reagent, GMBS (Calbiochem, La Jolla Calif.) and 5-iminothiolane HCl (Pierce Chemical Co., Rockford, Ill.) as described for phycoerythrin coupling by Hardy, supra. The heteroconjugate that resulted was separated from free antibody by Superose 6 (Pharmacia, Uppsala, Sweden) FPLC size exclusion chromatography and tested for reactivity with both CD3 and CD4 by testing the ability of the heteroconjugate to block the binding of directly fluorescein-conjugated anti-CD3 and anti-CD4 monoclonal antibodies. (column 17, lines 33-43).

Applicants respectfully submit that a heteroconjugate, as described by Ledbetter et al., refers to cross-linking of two monoclonal antibodies to form soluble dimers and/or oligomers ***and not*** to directly immobilizing a first and second agent on a solid phase surface as presently recited in claim 50. Thus, the instant claims 50-55 do not read on the prior art heteroconjugates and are not anticipated.

Furthermore, while Ledbetter et al. disclose a CD3/CD28 heteroconjugate comprising monoclonal antibodies G19-4 and 9.3 (column 24, lines 60-62), this heteroconjugate does not show any significant increase in its ability to activate T cells (as measured by intracellular calcium mobilization) over unstimulated or CD3/CD3-stimulated cells (see column 24, lines 63-67 and column 25, lines 1-34). This is in striking contrast to the CD3/CD2, CD3/CD4, CD3/CD6 and CD3/CD8 heteroconjugates, all of which cause a marked increase in calcium mobilization within the T cells treated with those heteroconjugates as compared to the activity of unstimulated or CD3/CD3-stimulated cells (column 25, Table III and lines 25-30). Thus, Ledbetter et al. actually ***teach away*** from using anti-CD3 and anti-CD28 to induce T cell proliferation, either as a heteroconjugate or immobilized on a solid surface, since the heteroconjugate of anti-CD3 and anti-CD28 antibodies does not stimulate T cell activation over background levels compared to heteroconjugates comprised of other cell surface marker combinations which support robust activation.

In summary, the bispecific antibodies and heteroconjugates described by Ledbetter et al. neither explicitly nor inherently disclose "a first and second agent directly immobilized on a solid phase surface" as required by the instant claims. Moreover, Ledbetter et al. teach away from using anti-CD3 and anti-CD28 immobilized on a solid surface to induce T cell proliferation. Thus, the claimed functional limitations would not be inherent properties of the referenced methods to stimulate T cell populations with heteroconjugates comprising anti-CD3 and anti-CD28 antibodies. Because Ledbetter et al. fail to teach or suggest ***each and every*** element of claim 50 and its dependent claims, Applicants respectfully request that the rejection made under 35 U.S.C. § 102(e) be withdrawn.

VII. Rejections under 35 U.S.C. § 103

Claims 50-55 and 57-58 stand rejected under 35 U.S.C. § 103 as being unpatentable over Ledbetter et al. (EP0440373) and/or Ledbetter et al. (U.S. Patent No.: 6,010,902) in view of Chang (U.S. Patent No.: 6,129,916) (Office Action, page 5, paragraph 10). Applicants respectfully traverse this rejection of claims 50-55 and 57-58 under 35 U.S.C. § 103.

The Examiner relies on the primary reference of Ledbetter et al. (EP0440373); "the '373 patent," to teach "methods of activating T lymphocytes with immobilized anti-CD3 and immobilized anti-CD28 antibodies." He admits that "Ledbetter et al. differ from the claimed methods by not exemplifying combining anti-CD28 and anti-CD3 antibodies on the same plate" but alleges that "Ledbetter et al. do teach combining both specificities to stimulate T cells and to immobilize both antibodies on plastic surfaces."

The Examiner alternatively relies on Ledbetter et al. (U.S. Patent No.: 6,010,902); "the '902 patent," to teach "compositions comprising heteroconjugates or bispecific antibodies comprising antibodies, including antibodies to human CD antigens involved in T cell activation, including antibodies to CD3 in combination with anti-CD28 antibodies (*e.g.*, 9.3), including compositions in order to stimulate T cell populations and subpopulations and reinfused in patients" and for teaching that "these cell populations have increased signal transduction, which can be measured by various known assays."

The Examiner relies on the secondary reference of Chang (U.S. Patent No.: 6,129,916); "the '916 patent," to teach "combining the particular CD3 and CD28 specificities, by teaching the use of microbeads and cross-linking by well-established manner (columns 7-8) in cross-linking anti-CD3 and anti-CD28 antibodies on microbeads to activate T cells in vivo." The Examiner alleges that although Chang focuses on the *in vivo* administration of stimulating immunoconjugates, "it was known

to stimulate T cells in vitro via immobilized stimuli" and further, that "both Ledbetter et al. references teach stimulating T cells for adoptive immunotherapy via CD3 and CD28 stimulation."

Finally, the Examiner alleges that "it was an art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made; as such criteria were known parameters of cell activation." He also holds that "it was common practice at the time the invention was made to re-activate and re-stimulate cells to maintain proliferation and expansion of cell populations of interest a the time the invention was made." Support for this allegation is apparently to be found in both the Ledbetter et al. references, which "teach methods of preparing cells for adoptive immunotherapy, which required large numbers of cells resulting from multiple stimulation."

To make a *prima facie* case of obviousness, the Examiner has the burden of showing either that some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Indeed, the prior art must suggest the combination or convey to those of ordinary skill in the art a reasonable expectation of success of making it. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The teachings of the references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 USPQ 929, 933 (Fed. Cir. 1984).

Claim 50, and claims depending therefrom, recite methods for inducing *ex vivo* ***proliferation*** of a population of T cells by contacting them with ***a solid phase surface immobilized with a first agent*** (*e.g.*, anti-CD3) which provides a primary activation

signal to the T cells, thereby activating the T cells; ***and a second agent*** (*e.g.*, anti-CD28) which stimulates an accessory molecule on the surface of the T cells, thereby stimulating the activated T cells, the first and second agents thereby inducing the T cells to ***proliferate***.

The '373 patent of Ledbetter et al. does not teach or suggest Applicants' invention as claimed and therefore cannot render it obvious. Ledbetter et al. teach methods for potentiating the development of ***CD3-independent cytolytic activity*** of lymphocytes to produce ***cytolytic*** lymphocytes by contacting the lymphocytes *in vitro* with an anti-CD28 antibody (page 2, lines 35-36, lines 40-42). They teach that anti-CD2 antibody or interleukin-2 may be added with the anti-CD28 antibody to the lymphocytes *in vitro* to achieve induction of ***cytolytic activity*** of lymphocytes (page 2, lines 49-50). Ledbetter et al. further disclose that immobilized anti-CD28 antibody may be used to maximize ***cytolytic response*** (page 2, lines 50-56; page 4, lines 10-11). In those instances where this reference teaches the use of two antibodies ***to induce cytolytic activity***, either both are soluble or one is immobilized and the other is in soluble form (page 8, lines 23-25).

However, as admitted by the Examiner (Office Action, page 5, paragraph 10, section 3) nowhere in the Ledbetter et al. reference is there a teaching or suggestion for ***directly immobilizing a first and second agent*** (for e.g., anti-CD28 and anti-CD3) on the ***same solid surface*** as required by the pending claims. More importantly, there is no teaching or suggestion for a method of inducing *ex vivo* ***proliferation*** of a population of T cells by contacting this population with ***a first and second agent directly immobilized on the same solid phase surface***.

To the contrary, Ledbetter et al. is directed to "stimulating the ***cytolytic activity*** of lymphocytes to kill tumor cells using anti-CD28 mAb reactive with the lymphocyte

receptor CD28" (page 3, lines 21-22). Stimulating cytolytic activity of lymphocytes is clearly distinct from a method of inducing a population of T cells to proliferate. That is, stimulating the cytolytic activity of T cells does not in any way, either explicitly or inherently, teach or suggest stimulating T cell proliferation. Accordingly, Ledbetter et al. do not teach a method of stimulating a population of T cells to ***proliferate*** using a first and second agent (for e.g. anti-CD3 and anti-CD28) directly immobilized on a solid surface.

Furthermore, the focus of the Ledbetter et al. reference is to potentiate a ***CD3-independent*** cytolytic activity, which clearly ***teaches away*** from Applicants' claimed method of inducing T cell proliferation described above, because it seeks to stimulate the cytolytic activity of lymphocytes in a wholly ***CD3-independent*** fashion. As such, Ledbetter et al.. do not render obvious Applicants' claims. In light of this argument, there would have been no motivation to combine the '373 patent of Ledbetter et al. with the additional references cited by the Examiner to provide the purported missing elements and arrive at Applicants' invention. Nevertheless, in order to be thorough, we will address the deficiencies of each of the secondary references cited by the Examiner.

The '902 patent of Ledbetter et al. does not remedy the deficiencies of each of the primary reference. This reference discloses novel heteroconjugates and bispecific antibodies. As detailed in the discussion in section VI above, Applicants respectfully assert that heteroconjugates and bispecific antibodies do not teach or suggest the use of ***a first and second agent directly immobilized on a solid surface.*** Heteroconjugates and bispecific antibodies are used in ***soluble*** form and thus are clearly ***not immobilized.*** As such, they do not in any way teach or suggest a first and second agent directly immobilized on a solid phase surface. Furthermore, this reference ***teaches away*** from using the combination of anti-CD3 and anti-CD28 antibodies since a CD3/CD28

heteroconjugate does not stimulate T cell proliferation over background levels as assayed by intracellular calcium mobilization. Thus, it provides no motivation whatsoever to directly immobilize anti-CD3 and anti-CD28 on a solid phase surface to induce T cell proliferation. In summary, the '902 patent of Ledbetter et al. in no way renders obvious Applicants invention as claimed but rather teaches away from it.

The '916 patent of Chang also does not remedy the deficiencies of the two Ledbetter patents. Chang discloses immunoregulatory conjugates including a polymeric backbone coupled with binding molecules, for example, antibodies or antibody-derived fragments which bind to monovalent antigenic epitopes on CD3, epitopes of the T cell receptor, or other antigens on the surface of T cells, *e.g.*, CD2, CD4, CD5, CD8, or CD28 (column 4, lines 39-52) or antibodies specific for HLA class-I antigens, HLA class II antigens, or anti-CD37 (column 11, lines 32-36) for use in activating T cells *in vivo*. There is no teaching or suggestion in Chang that would motivate an ordinary skilled artisan to select antibodies that bind CD3 and antibodies that bind CD28 among the laundry list of antibodies which are taught to be equally useful for activating T cells *in vivo*.

Furthermore, Chang ***teaches away*** from an ***in vitro*** method of activating T cells by teaching that a major concern with ***in vitro*** regimens

> is that the treatment is very tedious, expensive, and requires a sophisticated, specialized cell culture facility. The variation among cells or cultures from different patients requires demanding monitoring procedures. Also, ***lymphocyte cultures have very poor viability even under optimal conditions, meaning that during the culturing, large numbers of the cells will die.*** When large numbers of dead cells are injected into patients, this may actually burden the reticuloendothelial system (RES) and reduce its effectiveness in combating the tumor cells. [***emphasis added***]. See column 3, lines 19-27.

In addition, Chang teaches that ***in vitro*** and ***in vivo*** studies can have ***opposite*** outcomes:

> it has been suggested that the solid-phase anti-CD3 MAb functions by aggregating the CD3 antigen on the T cell surface. However, when anti-human CD3 is injected ***in vivo the results are the opposite of the in vitro effects***. OKT3 MAb, which is the first MAb ever approved for therapeutic use in vivo, is strongly immunosuppressive and is approved for use as an immunosuppressor for patients receiving kidney transplants. The injection of OKT3 causes rapid depletion of T cells from the circulation. [***emphasis added***]. See column 4, lines 3-13.

In view of the foregoing teachings by Chang, an ordinary skilled artisan would not find any teaching or any motivation to activate T cells *in vitro* with the Chang conjugates. Furthermore, based on the teachings in this reference, the ordinary skilled artisan would not have any expectation of success in extending Chang's *in vivo* studies *in vitro*.

The Examiner argues that it was an art known practice at the time of Applicants' invention to monitor cell proliferation by cell size and cell surface markers. He alleges that both Ledbetter references teach such methods because they obtain "large numbers of cells resulting from multiple stimulation." In particular he has pointed to the '373 patent of Ledbetter et al. for providing an example of culturing cells for three days (page 6, last paragraph). Applicants respectfully submit that the section of the European application that the Examiner refers to describes incubation of peripheral blood mononuclear cells (PBMCs) (untreated or pretreated with anti-CD16 mAb plus complement) with an immobilized anti-CD3 antibody for three days in the presence or absence of other soluble antibodies. The last paragraph at page 6, and for that matter the rest of the specification, of the '373 patent fails to teach or suggest monitoring cell proliferation by ***examining cell size*** or the ***level of expression of cell surface markers*** or a method for inducing a population of T cells to proliferate by contacting the T cells with

a first and second agent which are directly immobilized on the same solid surface, as required by Applicants' pending claims. Furthermore, nowhere in the '902 patent of Ledbetter et al. is there any teaching or motivation to cure the deficiencies of the '373 patent of Ledbetter et al.

Taken together, the proposed combination of references fails to teach or suggest with an expectation of success the invention as claimed in the currently pending claims. Applicants respectfully contend that the rejection of claims 50-55 and 57-58 under 35 U.S.C. § 103 is improper and request that it be withdrawn.

VIII. Provisional Rejection under the doctrine of obviousness-type double patenting

Claims 50-55 and 57-58 were provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 86-89, 92-94, 96, 102-106, 108-115, 118-120, 122, 128-131, 135-138, 141-148 and 150-167 of U.S. Serial No. 08/253,964; over claims 57-62, 69-72 and 75-77 of U.S. Serial No. 08/592,711; over claims 1, 46, 47, 54-58 and 69-72 of U.S. Serial No. 09/183,055; over claims 1, 50-55 and 57-58 of U.S. Serial No. 09/352,202; and over claims 10, 50-56, 58-67 and 69-84 of U.S. Serial No. 09/553,865.

While in no way admitting that claims 50-55 and 57-58 are obvious over the claims of the co-pending applications listed above, upon allowance of the claims of this application, Applicants will consider submitting a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c), if appropriate, which will obviate this rejection.

IX. Request for Ownership Information

The Examiner is of the opinion that claims 1, 46-47, 54-58 and 69-72 of the commonly assigned application, U.S. Serial No. 09/183,055 would form the basis for a

rejection of claims 50-55 and 57-58 of the instant application under 35 U.S.C. § 103 if the commonly assigned cases qualify as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In accordance with 37 C.F.R. § 1.78(c) the Applicants demonstrate that the inventions in the instant application and in U.S. Serial No. 09/183,055 were commonly owned at the time the invention in this application was made. Enclosed please find the Notice of Recordation documents showing that the instant application, U.S. Serial No. 09/349,915 filed July 8, 1999, was assigned by the inventors ("Assignors") to the indicated Assignees as follows:

Assignor(s):	Assignee:
Carl H. June	1) The United States of America, as represented by the Secretary of the Navy;
Craig B. Thompson Gary J. Nabel	2) The Regents of the University of Michigan;
Gary S. Gray Paul D. Rennert	3) Repligen Corporation.

Similarly, find also the Notice of Recordation documents demonstrating that U.S. Serial No. 09/183,055 filed October 29, 1998 were assigned by the inventors to the indicated Assignees as follows:

Assignor(s):	Assignee:
Carl H. June	1) The United States of America, as represented by the Secretary of the Navy;
Craig B. Thompson Gary J. Nabel	2) The Regents of the University of Michigan;
Gary S. Gray Paul D. Rennert	3) Repligen Corporation.

As the Examiner will readily note, the inventors as well as the Assignees are identical in both cases. Thus, Applicants believe that a potential 35 U.S.C. § 103 rejection in view of 35 U.S.C. § 102(f) or (g) has now been rendered moot.

X. Rejection under the doctrine of obviousness-type double patenting

Claims 50-55 and 57-58 stand rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No. 6,352,694.

While in no way admitting that claims 50-55 and 57-58 are obvious over the claims of U.S. Patent No. 6,352,694, upon allowance of the claims of the instant application, Applicants will consider submitting a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c), if appropriate, which will obviate this rejection.

XI. Conclusion

Applicants aver that all of the outstanding rejections of record have been overcome by amendment and/or argument. Accordingly, the claims are now believed to be in condition for allowance. Applicants respectfully request that the Examiner issue a timely Notice of Allowance.

No additional fees are believed to be due in connection with this correspondence. If any fees are due, please charge any payments due, or credit any overpayments, to our Deposit Account No. 08-0219.

The Examiner is invited to telephone the undersigned at the telephone number given below in order to expedite the prosecution of the instant application.

Respectfully submitted,

Colleen Superko
Reg. No. 39,850

Dated: May 28, 2003

HALE AND DORR LLP
60 State Street
Boston, MA 02109
Tel.: (617) 526-6564
Fax: (617) 526-5000